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REMARKS

Claims 1, 3, 7-29, 45, 47, and 51-73 are pending in this application. Claims 7, 26, 28, 70, and 72 have been amended. Support for these amendments can be found at least on pages 18-30. Applicant respectfully submits that no new matter has been added by way of these amendments.

As it now stands before the Patent Office, Claim 1 recites, among other things, a method for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit. Claims 2 and 4-6 have been canceled without prejudice or disclaimer. Claims 3 and 7-29 depend directly or indirectly from independent Claim 1.

Claim 45 recites, among other things, a method for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder by administering in a combination therapy methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit, wherein the amount of the methyltestosterone and the steroid together make a menopause disorder effective amount. Claims 46 and 48-50 have been canceled without prejudice or disclaimer. Claims 47 and 51-73 depend directly or indirectly from independent Claim 45.

***35 U.S.C. § 112 Rejection***

Claim 7 stands rejected under 35 U.S.C. § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses the rejection and requests withdrawal of the same. Claim 7 has been amended to depend from Claim 1. Applicant respectfully submits that the § 112 second paragraph rejection has been overcome.

***35 U.S.C. § 103(a) Rejections***

Claims 1, 3, 7-13, 20-27, 45, 47, 51-57, and 64-71 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Rubin (US Patent 5,059,603), Ebert et al. (US Patent 5,152,997), and AndroGel Monograph from IDS of December 9, 2002 in view of Langtry et al. (Drugs 1999: 57(6): 967-989), Leucuta et al. (abstract of Clujul Medical, 1983: 56(4): 371-376), and Rheology Modifiers Handbook (2000, pages 81-88, published by William Andrew Publishing). Applicant respectfully traverses the rejection and requests withdrawal of the same.

Rubin, Ebert et al., and AndroGel Monograph in view of Langtry et al., Leucuta et al. and Rheology Modifiers Handbook do not teach or suggest the claimed invention. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990)).

Rubin indeed discloses that impotence associated with androgen deficiency has long been thought to be treatable by administering male hormones such as the synthetic methyltestosterone. *See* col. 2, ll. 59-64. However, rather than teach methyltestosterone as useful in such treatment as the Examiner suggests, Rubin cautions that the administration of exogenous hormones has pharmacologic disadvantages. In fact, Rubin teaches away from using methyltestosterone because subcutaneously or buccally taken methyltestosterone “may cause severe toxic effects such as cholestatic jaundice” and parenterally administered testosterone esters have drawbacks such as “additional pain, lack of complete absorption, and risk of deep and widespread infection.” *See* col. 3, ll. 1-7.

Moreover, Rubin adds that “long-term administration of these synthetic compounds [i.e., methyltestosterone] may inhibit endogenous testosterone formation and spermatogenesis by

suppressing pituitary gonadotropin, resulting in glandular tissue atrophy because of disuse.” *See* col. 3, ll. 7-11. Consequently, Rubin does not teach or suggest methyltestosterone to treat androgen deficiency associated disorders such as impotence.

Ebert et al. disclose a transdermal composition including testosterone, a permeation enhancer, and polymer matrix in treating male hypogonadism. *See* col. 1, ll. 21-66. However, Ebert et al. conclude that “the art teaches away from transdermally administering testosterone through nonscrotal skin because of the low permeability of such skin to testosterone” and that transscrotal delivery, although taught, “does not provide a level of testosterone delivery that mimics endogenous production.” *See* col. 2, ll. 22-32. Thus, contrary to the Examiner’s assertion, Ebert et al. do not teach or suggest the claimed combination therapy.

Langtry et al. discloses that sildenafil is useful in treating erectile dysfunction, as the Examiner notes. Langtry et al., however, do not teach or suggest combining sildenafil with methyltestosterone to treat menopause disorders as in the claimed invention.

Similarly, Leucuta et al. do not teach or suggest using a combination therapy of methyltestosterone in an oral dosage form and testosterone (or estradiol) in a topical form. Leucuta et al. disclose only that methyltestosterone oral tablets were comparable to methyltestosterone sublingual tablets in release rate, provided that each oral tablet contains 25-30 mg of methyltestosterone, and that bioavailability of methyltestosterone increased at 30 mg as compared to 20 mg.

The AndroGel Monograph does not teach the claimed combination. Finally, Rheology Modifiers Handbook does not teach or suggest the claimed combination therapy.

In sum, Rubin, Ebert et al., and AndroGel Monograph in view of Langtry et al., Leucuta et al., and Rheology Modifiers Handbook do not teach or suggest the claimed invention of a

method for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Contrary to the Examiner's suggestion, one of ordinary skill in the art would not be motivated to combine testosterone, methyltestosterone, and sildenafil to treat menopause disorders. The cited references lack motivation to combine their teachings to achieve the claimed invention.

Admittedly, virtually all inventions are combinations of old elements. *In re Rouffet*, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998). But the Examiner here has engaged in impermissible hindsight reconstruction by using the present application as a template for combining the cited references.

To uphold a § 103 rejection, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* The Examiner has not identified any motivation to combine the cited references. Applicant respectfully submits that the cited references lack any motivation to combine their teachings to achieve the present invention. The 35 U.S.C. § 103(a) rejection is therefore improper. Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 1, 3, 14-23, 28-29, 45, 47, 58-67, and 72-73 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Place (US Patent 6,117,446) in view of Remington's Pharmaceutical Sciences (1990, 18<sup>th</sup> ed., pages 1305 and 1314), Merck Index (11<sup>th</sup> ed., 1989,

page 821, monograph 5103), Leucuta et al. (abstract of Clujul Medical, 1983: 56(4): 371-376), and Rheology Modifiers Handbook (2000, pages 81-88, published by William Andrew Publishing).

Place in view of Remington's Pharmaceutical Sciences, Merck Index, Leucuta et al., and Rheology Modifiers Handbook do not teach or suggest the claimed invention.

Place teaches the administration of an androgenic agent with a progestin and an estrogen in a buccal dosage unit to provide a complete hormone replacement therapy for women.

Remington's Pharmaceutical Sciences teaches that ethanol may be used externally in astringent and anhidrotic lotions, as a solvent to cleanse the skin, and as an antiseptic for the skin and for instruments. The Merck Index teaches that isopropyl myristate may be used in topical medicinal preparations where good absorption through the skin is desired.

Leucuta et al. disclose that methyltestosterone oral tablets were comparable to methyltestosterone sublingual tablets in release rate, provided that each oral tablet contains 25-30 mg of methyltestosterone, and that bioavailability of methyltestosterone increased at 30 mg as compared to 20 mg. Leucuta et al. do not teach or suggest using a combination therapy of methyltestosterone in an oral dosage form and testosterone in a topical form.

Not one reference cited teaches using estradiol as a topical gel and methyltestosterone in an oral dosage form to treat female menopausal disorders. The Examiner simply asserts that one of ordinary skill in the art would have been motivated to combine the two agents in exactly the forms and in exactly the dosages as in the claimed invention.

The Examiner has pointed to no reasons that would motivate one of ordinary skill in the art, when confronted with the same problems as those faced by Applicant and with no knowledge

of the claimed invention, to select the elements from the cited references and combine them as in the claimed invention. *In re Rouffet*, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998).

Applicant respectfully submits that the foregoing references do not teach or suggest, either alone or in combination, a method for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit. The Examiner does not cite any references showing or suggesting the combination of elements in the manner recited in Claims 1, 3, 7-29, 45, 47, and 51-73. The 35 U.S.C. § 103(a) rejection is therefore improper, and Applicant requests reconsideration and withdrawal of this rejection.

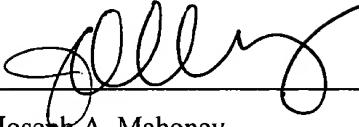
#### CONCLUSION

With entry of the above Amendment and in view of the foregoing Remarks, Applicant respectfully submits that all of the objections and rejections in the Office Action dated February 26, 2003 have been overcome and should be withdrawn, and that claims 1, 3, 7-29, 45, 47, and 51-73 are now in condition for allowance. Applicant respectfully requests early and favorable notification to that effect.

None of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicant reserves all rights to pursue any such subject matter in this or a related patent application. If, in the opinion of the Examiner, a phone call may help to expedite prosecution of this application, the Examiner is invited to call Applicant's undersigned attorney at (312) 701-8979.

Respectfully submitted,

Dated: July 25, 2003

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